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| REEVES, J | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

1- File Copy

PTO-90C (Rev. 2/95)
*U S GPO 1998-437-638/80022

| Office Action Summary | Application No 08/817,507 | Applicant(s) Kishimoto et al |
|---|---|---|
| | Examiner Julie E. Reeves, Ph.D. | Group Art Unit 1642 |

☒ Responsive to communication(s) filed on *Jan 6, 1999*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *15-28* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *15-28* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

1. Claims 1-14 have been canceled. Claims 15-28 have been added and are under examination.

### *Election/Restriction*

2. Applicant's election with traverse of Group I in Paper No. 11 is acknowledged. The traversal is on the ground(s) that all the groups depend upon the same basic mechanism, i.e. the use of an antibody that binds to the IL-6 receptor. This is found persuasive and accordingly the restriction requirement has been withdrawn. Claims 15-28 are under examination.

3. The text of those sections of Title 35, U.S.C. Code not included in this Office Action can be found in a prior Office Action.

4. The response to the 102 and 103 rejections set forth on page 5-6 have been considered carefully but are deemed moot in view of the fact all the claims directed to the pharmaceutical composition have been canceled and replaced with claims directed to methods of treatment. This Office Action contains some new grounds of rejection which have been necessitated by amendment.

### *Specification*

5. The new title is sufficiently descriptive.

6. The disclosure is objected to because of the following informalities: The first line of the specification needs to be amended to show that this application is a 35 U.S.C. 371 national stage

filing of international application PCT/JP95/02169 filed 10/20/95. The amendment provided by Amendment B, Paper no 10 is insufficient because the phrase "this application is a 35 U.S.C. 371 national stage filing of" is lacking. Appropriate correction is required.

***Information Disclosure Statement***

7. It is noted that Applicants have cited a reference in their response filed 10/13/98. This reference not been made of record on a PTO 1449 and will not be cited on the face of the file once the application goes on to issue as a patent. Should Applicant wish to have this reference made of record, it is suggested that Applicant file a PTO 1449 citing the reference.

***Claim Objections***

8. Claims 18, 25 and 28 are objected to because of the following informalities: the terms "Castleman's" (claim 18) and "hybridoma" (claims 25 and 28) are apparently misspelled . Appropriate correction is required.

***Claim Rejections - 35 U.S.C. § 112***

9. Claims 15-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 15-28 are indefinite for reciting in claim 15 "administering a therapeutically effective amount of an antibody to an IL-6 receptor" because the claim does not provide a functional limitation for the effective amount. Amendment the claim to recite "wherein the

therapeutically effective amount blocks signal transduction by IL-6 and inhibits the binding of IL-6 to the IL-6 receptor" would be sufficient to obviate this rejection. Support for this amendment is found, for example, on pages 3-4, bridging paragraph of the specification.

10. The rejection of newly added claims 25 and 28 under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description has been made again and maintained. The response set forth on page 4, paragraph 3.1 and the Supplemental Amendment under 37 CFR 1.111, 12/2/98 as Paper no 10 1/2 has been considered carefully but is deemed not to be persuasive.

Applicant's referral to the deposit of the PM-1 hybridoma on page 1 of paper no 10 1/2 or on page 4, paragraph 3.1 of Paper no 10 is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 have been met.

Because the PM-1 deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit of the PM-1 hybridoma has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on

this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

Amendment of the specification to recite the date of deposit and the complete name and full address of the depository is required. Applicant's attention is directed to In re Lundak, 773 F. 2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

11. The rejection of newly added Claims 15-28 under 35 U.S.C. 112, first paragraph, has been withdrawn in view of the response set forth on pages 4-5, taken in view of the Japanese Journal of Clinical Immunology reference (Nishimoto et al 20(2) 87-94 1997, attached to paper no 10). The 1997 publication provides evidence that the animal models in the specification were predictive and could be correlated to the outcome in humans.

***Claim Rejections - 35 U.S.C. § 102***

12. Claims 15, 16, 19, 24 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Suzuki et al (Eur J Immunology Vol 22 1989-1993, published in 1992), as evidenced by Robbins (Pathological Basis of Disease, Fifth Edition, 1994) and as evidenced by HarpersCollins Illustrated Medical Dictionary (1993).

a. Newly added claim 15 recites a method of treating a subject having a disease caused by IL-6 production comprising administering to said subject a therapeutically effective amount of an antibody to IL-6 receptor in a pharmaceutically acceptable carrier. Claim 16 recites a method of claim 15, wherein the disease is plasmacytosis. Claim 19 recites wherein the disease is hyperimmunoglobinemia. Claim 24 recites wherein the antibody is a monoclonal antibody. Claim 25 recites wherein the antibody is the PM-1 antibody.

b. It is noted that the term "subject" in claim 15 broadly encompasses the administration to an animal, such as a SCID mouse. The term "plasmacytosis" (claim 16) is defined as "the presence of plasma cells in the blood or abnormally large percentage of plasma cells in the tissues" (see HarperCollins, page 378). It is noted that the clinical course of multiple myeloma is described as "(1) infiltration of organs, particularly bones by the neoplastic plasma cells and (2) the production of excessive immunoglobulins" (see Robbins, page 664, first full paragraph). The condition of "hyperimmunoglobulinemia" recited in claim 19 results from the production of excessive immunoglobulins.

c. Suzuki et al specifically teaches that "PM1 inhibited IL-6 dependent growth of a human T lymphoma, IL-6 mediated antibody production in B cell line SKW6CL4 and IL-6 mediated growth of human myeloma cell line *in vitro*" (page 1991, first full paragraph). Suzuki et al teach that the "first report on the clinical use of anti-human IL-6 antibody trial showed that injection of mAb to multiple myeloma patients with terminal diseases completely blocked the myeloma cell proliferation *in vivo*" (page 1991, col 2, first full paragraph). Suzuki et al teach the

administration of an anti-human IL-6 receptor antibody PM-1 which "clearly inhibited human myeloma cell growth in mice" (page 1992, first full paragraph). Also see Figures 3-5. Thus the teachings of Suzuki et al, as evidenced by the dictionary and textbook definitions provided above, taken in view of the interpretation of the phrase "treating a subject", meet the limitations of the claims as written.

***Claim Rejections - 35 U.S.C. § 103***

13. Claims 15-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al, as evidenced by Robbins (1994) and HarpersCollins Illustrated Medical Dictionary (1993), as applied to claims 15, 16, 19, 24, 25 above, and further in view of Sato et al (Cancer Research Vol 53, 851-856 2/93, of record).

a. Claims 15, 16, 19, 24 and 25 have been described above. The dictionary and textbook definitions for plasmacytosis and hyperimmunoglobulinemia have been discussed above. Claim 17 recites wherein the disease is rheumatism. Claim 18 recites wherein the disease is Castleman's disease. Claim 20 recites wherein the disease is anemia. Claim 21 recites wherein the disease is nephritis. Claim 22 recites wherein the disease is mesangium proliferative nephritis. Claim 23 recites wherein the disease is cachexia. Claim 26 recites wherein the antibody comprises a murine variable domain and human constant domains. Claim 27 recites wherein the antibody is humanized murine monoclonal antibody. Claim 28 recites wherein the humanized antibody is humanized PM-1 antibody.

b. As evidenced by Robbins, patients "with cancer commonly suffer progressive loss of body fat and lean body mass accompanied by profound weakness, anorexia and anemia. This wasting syndrome is referred to as cachexia" (page 295, first full paragraph). Thus one skilled in the art would reasonably expect that a method which treats cancer would also ameliorate the symptoms of cancer, including cachexia and anemia as recited in claims 23 and 20, respectively.

c. The teachings of Suzuki et al have been discussed above. Suzuki et al does not explicitly teach the administration of an anti-IL-6 receptor antibody for the treatment of rheumatism, Castleman's disease, nephritis, mesangium proliferative nephritis, cachexia or anemia. Suzuki et al does not teach the administration of 1) an antibody which comprises a murine variable domain and human constant domains, 2) humanized murine monoclonal antibody or 3) a humanized antibody is humanized PM-1 antibody.

d. However, Suzuki et al does teach that the administration of an PM-1 anti-IL-6 antibody inhibits the IL-6 dependent growth of human multiple myeloma cells *in vivo*. Suzuki et al also explicitly teach that the diseases rheumatoid arthritis, Castleman's disease and mesangial glomerulonephritis (a form of nephritis) are also associated with the abnormal production of IL-6 (page 1989, first full paragraph). Thus Suzuki et al provide a basic mechanism linking the various diseases and symptoms recited in the claims.

e. Sato et al teach that mouse antibodies are highly immunogenic in human patients (page 851, col 1, second full paragraph). Sato et al teach that the reshaped humanized PM-1 antibody, the chimeric PM-1 antibody and the murine monoclonal antibody PM-1 were equivalent

"in terms of antigen binding and growth inhibition against multiple myeloma cells" (see Abstract). Sato et al's chimeric PM-1 antibody comprised human constant regions and murine variable domains (see page 851, col 2, "Construction of Chimeric Antibody"). Sato et al also explicitly teach that the diseases plasmacytosis/myeloma and mesangial proliferative glomerulonephritis (a form of nephritis) are also associated with the abnormal production of IL-6 (page 851, first full paragraph). Thus Sat et al provide a basic mechanism linking the various diseases and symptoms claimed. Sato et al teach that a mouse monoclonal antibody used in a clinical study against human IL-6 to treat a primary plasma cell leukemia blocked in myeloma cell proliferation (page 851, first full paragraph). Sato et al explicitly state that "the reshaped human PM-1 antibody is expected to be useful as a therapeutic agent in human multiple myeloma patients" (page 855, final paragraph).

f. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have administered the chimeric or reshaped humanized PM-1 antibody of Sato et al which binds to the IL-6 receptor to patients suffering from a disease caused by IL-6 production 1) because Suzuki et al teach that administration of PM-1 antibody to SCID mice inhibited the growth of IL-6 dependent myeloma cells *in vivo*; 2) because Suzuki et al and Sato et al specifically point to other diseases including rheumatoid arthritis, mesangial proliferative glomerulonephritis, plasmacytoma and Castleman's disease which depend upon the same basic mechanism of abnormal IL-6 production and 3) because Suzuki et al provide a reshaped humanized PM-1 antibody which "inhibits multiple myeloma cell growth as well as the original mouse PM-1 antibody does *in vitro*" (page 855, final paragraph).

g. One of ordinary skill in the art would have been motivated to use the chimeric or humanized PM-1 antibody of Sato et al in the treatment of patients suffering from disease caused by IL-6 production 1) because the "reshaped PM-1 antibody looks very like a human antibody and is expected to be a poor immunogen in human patients" (Sato et al, page 855, second full paragraph); 2) because it was known that for repeated administration, "mouse antibodies must be engineered to look like human antibodies" (Sato et al page 851, second full paragraph) and 3) because the reshaped, chimeric are equivalent to the murine antibody "in terms of antigen binding and growth inhibition against multiple myeloma cells" (Sato et al, Abstract).

h. Moreover, one of ordinary skill in the art would have been motivated to use the PM-1 antibody to treat other diseases caused by IL-6 production, including rheumatoid arthritis, Castleman's Disease and mesangial proliferative glomerulonephritis, because Suzuki et al recite such as list of disease and suggest that "the administration of an inhibitor of IL-6 may be of clinical use" (page 1989, first full paragraph). Similarly one of ordinary skill in the art would have been motivated to use the PM-1 antibody to treat other diseases caused by IL-6 production, because Sato et al recite a list of diseases, including plasmacytosis and mesangial proliferative glomerulonephritis linked by abnormal L-6 expression and state that antibodies which inhibit IL-6 functions "are expected to be useful as therapeutic agents in human patients" (page 851, first full paragraph). Therefore the art teaches that the variety of diseases and symptoms recited in the claims are caused by the same basic mechanism i.e., abnormal IL-6 production. Given the success that Suzuki et al had in ameliorating the symptoms and disease of the IL-6 dependent

multiple myeloma cells in SCID mice, one skilled in the art would reasonably expect that by targeting the mechanism of abnormal IL-6 production with an anti-IL-6 receptor antibody, other diseases and symptoms would be ameliorated. This position is supported by the fact that a mouse monoclonal antibody against IL-6, which blocks the binding of IL-6 to the IL-6 receptor, also blocked myeloma cell proliferation in a human patient (Sato et al, page 851, first full paragraph).

i. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success using either the chimeric or reshaped PM-1 antibodies to treat subject having a disease caused by IL-6 production 1) because Suzuki et al successfully demonstrated the inhibition of human myeloma cell growth in the SCID mouse model system by administering the murine PM-1 antibody; 2) because Sato et al's reshaped and chimeric PM-1 antibodies retained equivalent antigen binding and growth inhibition properties as the murine PM-1 antibody and 3) because Sato et al summarize that the "reshaped human PM-1 antibody is expected to be useful as a therapeutic agent in human multiple myeloma patients" (page 855, final paragraph).

j. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success of treating other diseases caused by IL-6 production, including rheumatism, Castleman's's disease, nephritis, mesangial proliferative nephritis, anemia and cachexia because both of Sato et al and Suzuki et al, while exemplifying the IL-6 dependent disease myeloma, along with the suggestion of using an anti-IL-6 receptor antibody to block IL-6 binding to the IL-6 receptor, in general, provide a listing of other diseases caused by IL-6 production.. One skilled in the art would reasonably expect that treatments which target the basic mechanism of IL-6

receptor binding would also ameliorate the symptoms of the various diseases. For example, a treatment which blocks myeloma cell growth *in vivo* would also ameliorate other cancer-associated symptoms such as cachexia and anemia. See Robbins for the evidence that anemia and cachexia are symptoms or diseases of cancer.

k. Additionally, it is noted that Applicant's representative persuasively stated in the response to the Restriction Requirement "that the five alleged separate depend upon the same basic mechanism, i.e., the use of an antibody that binds an IL-6 receptor" (see Paper no 12, filed 1/6/99).

14. No claims are allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Reeves, Ph.D., whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Julie C Reeves

Julie E. Reeves, Ph.D.

Patent Examiner

JULIE REEVES
PATENT EXAMINER

(703) 308-7553